to a method for obtaining a composition for pharmacological use from an unmodified dextran.

REMARKS

Claims 35, 36, 45, 57 and 59 are herein amended. As of this amendment, claims 1-13, 18-29, 35-36, and 39-66 are pending. Below we address first the rejections based on prior art and second the rejections based on 35 U.S.C. §§ 132 and 112.

I. The combinations of prior art references urged by the examiner in rejecting the claims under 35 U.S.C. § 103 ignore problems with instability and adverse reaction risks associated with such combinations

In addressing the prior art rejections, it is desirable to consider first the claimed subject matter that stands rejected for obviousness. Various claims are addressed to methods of providing an iron oxide complex for administration to a subject. As discussed in further detail below, the preamble limitation is "for administration to a mammalian subject" (see e.g. claims 1 and 5). In the invention defined by these claims the phrase "for administration to a mammalian subject" informs the person of ordinary skill in the art that the iron oxide complex must have an acceptable profile with respect to stability and risk of adverse reaction, and if the mammal is a human, must typically be approved by a regulatory authority such as the Food and Drug administration.

A. No one disputes the desirability of autoclaving for achieving sterilization of materials for administration.

There is no question that it would be highly desirable, from both regulatory and commercial perspectives, to have a polysaccharide superparamagnetic iron oxide

complex as a pharmaceutical that when terminally sterilized (autoclaved) does not form particulates and that has minimal adverse reactions. Lewis Declaration, par. 3.

As pointed out by Dr. Lewis, "the United States Food and Drug Administration and its European counterpart have a policy that strongly favors terminal sterilization (autoclaving) over filter sterilization. The reason for this policy is that terminal sterilization provides a much higher level of sterility assurance than does filter sterilization" (citations omitted). Lewis Declaration, par. 4.

Indeed, "polysaccharide superparamagnetic iron oxide complexes are opaque, and their nature prevents ordinary visual inspection by the end user (the physician) for the presence of microbial contamination. This factor makes it even more important to provide assurance of sterility, and thus makes terminal sterilization even more important." Lewis Declaration, par. 5.

B. However, autoclaving polysaccharide iron oxide compositions creates the dual risk of particulates (requiring at a minimum filtration during administration) and adverse reactions (requiring at a minimum dilution and slow administration).

Despite the desirability of terminal sterilization (autoclaving), Dr. Lewis shows that "terminal sterilization of polysaccharide superparamagnetic iron oxide complexes creates serious problems. These problems show up in the history of the development of such materials. Advanced Magnetics, Inc., where [Dr. Lewis has] worked as a scientist for more than 15 years, has pioneered this development, as shown in the patents awarded to Advanced Magnetics in this field." Lewis Declaration, par. 6. This history, discussed below, shows that autoclaving creates a risk of particulates, and, as a result, at a minimum it is required in the prior art to filter the material during administration. This history also shows that autoclaving creates a risk of adverse reactions, and, as a result, at

a minimum, the material must be diluted prior to administration and administered only slowly.

1. Feridex (Groman patent) is autoclaved, but at the expense of filtration during administration, and requiring dilution and slow administration.

Dr. Lewis tells of an early product developed by Advanced Magnetics, now sold as Feridex®, which is the first commercial material of its type to be approved by the FDA. Lewis Declaration, par. 7. Aspects of this material are disclosed in the Groman patent cited by the examiner, U.S. patent 4,827,945 Lewis Declaration, par. 7. Dr. Lewis is a co-inventor of this patent, which is assigned to Advanced Magnetics, Inc., the assignee of the present application. *Id.* Feridex® is terminally sterilized. *Id.* "However, to permit the material to be terminally sterilized, citrate must be added. U.S. patent 4,827,945, col. 9, lines 26-32; col. 29, lines 15-36. Even with the addition of citrate, the material has an associated risk of particulate formation, which must be addressed in administration of the material. In particular, the material must be filtered at the time it is administered to the patient to assure removal of these particulates. Another risk associated with the material is that of adverse reactions, measured in laboratory animal experiments as edematous response. Owing to the risk of adverse reactions, the material is administered only after dilution and is also administered slowly." Lewis Declaration, par. 7 (reference to package insert omitted).

2. Combidex (Josephson patent) is not autoclaved at all, even though known to be a superior method of sterilization. Moreover, even with filter sterilization, it must be filtered during administration and requires dilution and slow administration.

After Feridex®, the second generation of commercial material developed by Advanced Magnetics was Combidex®. Lewis Declaration, par. 8. This material, which is

a complex of ultrasmall particles, which have a different biodistribution due to their smaller size, has received an approvable letter from the FDA. Lewis Declaration, par. 8. Aspects of this material are disclosed (among other places) in the Josephson patent cited by the Examiner, U.S. patent 5,160,726. Lewis Declaration, par. 8. Given the fact this is an improved material, one would expect it to be autoclaved, but Dr. Lewis points out that this is not the case. "Despite the fact that this is a second generation material and the regulatory policies favoring terminal sterilization, this material is sterilized by filtration, not by terminal sterilization (i.e, not by autoclaving), in order to have satisfactory stability. See, for example, abstract and passim of U.S. patent 5,160,726. Furthermore, the use of filter sterilization here does not obviate the associated risk of particulate formation, which, as in the case of Feridex®, must be addressed in administration of the material. In particular, the material must be filtered at the time it is administered to the patient. Another risk associated with the material, as in the case of Feridex®, is that of adverse reaction, measured in laboratory animal experiments as edematous response. Owing to the risk of adverse reactions, the material is administered only after dilution and is also administered slowly." Lewis Declaration, par. 8.

> 3. The subject matter herein concerns a third generation material, which overcomes the problems of particulate formation and adverse reaction associated with the first two generations of material.

Dr. Lewis and his colleagues have developed a third generation of material, to which the present application is directed, now in clinical trials. Lewis Declaration, par. 9. "This material, like Combidex®, is a complex consisting of ultrasmall particles and has a similar favorable biodistribution. This material is terminally sterilized, and unlike

Feridex® and Combidex®, has a sufficiently small risk of particulate formation that no filtration is required during administration." Lewis Declaration, par. 9.

Additionally, the risk of adverse reaction (measured in laboratory animal experiments as edematous response) associated with the new material is significantly lower than in the case of Feridex® and Combidex®. This lower risk means that (unlike Feridex® and Combidex®) the material can be administered more rapidly and without dilution. The analysis set forth above for Feridex®, Combidex®, and the new material is summarized in the following table (Lewis Declaration, par. 10):

Material	**Sterilization method**	**Does particulate formation risk require filtration during administration?**	**Does adverse reaction risk require dilution and slow administration?**	**Edematous response?**
Feridex (Lewis, 5,055,288; Groman, 4,827,945)	Autoclaving following citrate addition	Yes	Yes	Yes
Combidex (Josephson, 5,160,726)	Filtration	Yes	Yes	Yes
New material (in present application)	Autoclaving	No	No	No

Other MRI contrast agents (which are not iron-based) already utilize autoclaving for terminal sterilization, thereby allowing more concentrated administration of the contrast agent, and providing a safer agent with a higher assurance of sterility. As stated by Dr. Lewis, ".... we note that other commercial contrast agents such as gadolinium based MRI contrast agents and iodine based CT contrast agents are all sterilized by autoclaving and are administered without a filter or dilution all in compliance with the

preferred regulatory requirements. Furthermore we note that not having to use a filter and being able to deliver these contrast agents without dilution serve commercial and medical needs also." Lewis Declaration, par. 11. In other words the new material claimed in the present application provides new properties, never before available, in polysaccharide superparamagnetic iron oxide complexes.

C. The preamble limitation in the claims herein, calling for administration to a mammalian subject, cannot be ignored.

As stated by the Federal Circuit in *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d. 1298, 1305 (Fed. Cir. 1999), "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim. In the present invention, the preamble limitation to a method of providing an iron oxide complex is "for administration to a mammalian subject" (see claims 1 and 5). This limitation is not merely a statement of purpose. As held in *Kropa v. Robie* (187 F.2d 150, 152 (CCPA 1951)) "it is only by that phrase that it can be known that the subject matter defined by the claims is comprised as an abrasive article. Every union of substances capable *inter alia* of use as abrasive grains and a binder is not an 'abrasive article." In the present invention, it is by that phrase "for administration to a mammalian subject" that one knows that the iron oxide complex must have an acceptable profile with respect to stability and risk of adverse reaction, and if the mammal is a human, must be approved by a regulatory authority such as the Food and Drug administration. Every iron oxide complex will not meet the requirements of the claim – that is, the complex must be one that can be administered to a mammalian subject.

As claims 1 and 5 require, the method of providing an iron oxide complex for administration to a mammalian subject involves the step of sterilizing the complex by autoclaving. Maruno 1 (US 5,204,457) does not teach a method for administration of an iron oxide complex to a mammalian subject that utilizes autoclaving as the sterilization means. Dr. Lewis reiterates this position, stating "There is no teaching in Maruno of how to make stable materials that survive autoclaving. Nor is there any teaching in Maruno of materials that have decreased adverse reactions (measured in laboratory animal experiments as edematous response)." Lewis Declaration, par. 12.

In fact, Maruno 1 teaches away from autoclaving. There is no dispute that Maruno uses filter-sterilization to sterilize the iron oxide contrast agents. See, for example, patent 5,204,457, col. 15, lines 30-50 (Example 1 and Table 2); col. 16, lines 1-10 (Reference Example 4 and Table 3 use Example 1 procedures); and *passim*. See also, for example, patent 6,165,378, col. 17, lines 12-14 and 38-43; and col. 18, lines 9-13 and lines 48-50. Dr. Lewis explains why. "Given the well-established and clear preference for terminal sterilization (autoclaving) discussed above, the only reason for using filter sterilization instead of terminal sterilization is the instability of the material as resulting from exposure to the relatively high temperature required for autoclaving." Lewis Declaration, par. 13.

In support of this explanation, Maruno 1 states, "in the stability-in-preservation test wherein the complex aqueous sol of the invention is preserved at 55° to 80°C.... no external change is observed for one month or more to six months or more, whereas when the complex aqueous sol synthesized using NaOH-treated modified dextran is preserved under the same conditions, the deposition of precipitate or gelation is observed 3 to 10

days later. *Similar tendency is observed in an autoclave at 110° to 130°C* (sterilization with heating)." See col. 11, lines 12-14 and 25-32. The similar tendency observed is deposition of *a precipitate* or gelation, undesirable results that would result in adverse affects if such complexes were administered to a mammalian subject, because, as explained in Lewis (US 5,055,288) "Frankly particulate materials, ... are quickly removed from the blood by the phagocytic action of the cells of the reticuloendothelial system. .... All particulate agents suffer a similar limitation." See col. 3, lines 5-9 and 12-13. Thus, Maruno 1 does not meet the requirement of the preamble claimed in the present invention, because the materials of Maruno 1 do not meet the FDA objectives of being terminally sterilized. Further, they are subject to gelation and/or deposition of particulates.

In fact, Maruno 1 describes preparing the complex of the invention wherein "the aqueous sols were filtered with a membrane filter of 0.45 μm and the filtrates were charged into 5 ml ampoules. These ampoules were preserved at 80 ± 2°C." See col. 18, Example 1. As pointed out by Dr. Lewis, "The absence of testing data above 80 degrees C, in combination with the use of filter sterilization, confirms, to a person of ordinary skill in the art, that the materials are indeed subject to precipitation or gelation at higher temperatures." Lewis Declaration, par. 13. Thus, one of ordinary skill in the art would not have motivation to combine Maruno 1 with Lewis.

D. There is no motivation to combine Maruno 1 or Maruno 2 with any cited reference.

The Josephson patent (US 5,160,726) reiterates the desirability of autoclaving for sterilizing materials for administration to a mammalian subject, stating:

> The preferences for terminal sterilization over filter sterilization on the basis of sterility assurance, the generally low acute toxicity observed with terminally sterilized iron oxide preparations, and the difficulty of visually detecting microbial contamination, all combine to suggest that terminal sterilization is the method of choice for parenteral superparamagnetic iron oxide colloids. (col. 3, lines 50-57).

Similarly, the Declaration by inventor Jerome M. Lewis, Ph.D., states the same ideal (see section 3.) However, the Josephson reference goes on to warn that "The current invention involves the surprising observation that terminal sterilization can modify superparamagnetic iron oxide colloids so that a drop in blood pressure (a highly undesirable adverse reaction) is more likely to result from their administration." See col. 3, lines 62-67.

The present inventors, aware of the possibility of such "highly undesirable adverse reaction(s)" claim (among other things) "An improved method of administering to a mammalian subject a polysaccharide wherein there is a risk of edematous response, the improvement comprising....." (see amended Claim 36) and then "A method according to claim 36, further comprising sterilizing the composition by autoclaving." (see claim 39). Such claimed subject matter runs contrary to the warnings of Josephson, and contradicts what a person of ordinary skill in the art would normally do – heed the warnings of Josephson and thus not substitute autoclaving for filtration as the method of terminal sterilization.

Further, Maruno 2 provides support for heeding Josephson's warning. Maruno 1 was filed in 1991 and disclosed filtration as the method for sterilization. Josephson was also filed in 1991 and pointed out that autoclaving was preferred, but warned of adverse reactions if one, in fact, used it for sterilization. Maruno 2 (US 6,165,378) was filed in 1998 and 7 years later still discloses filtration as the method for sterilization (see col. 17,

lines 8-13). In fact, Maruno 2 "despite the fact of having been filed 7 years later, contains no testing data whatsoever for stability at elevated temperatures." Lewis Declaration, par. 13. This suggests that one of ordinary skill in the art would not combine Josephson with Maruno 1 to substitute autoclaving for filtration because even Maruno did not substitute autoclaving for filtration in the Maruno 2 patent. As emphasized by Dr. Lewis, "autoclaving normally requires temperatures of at least 121 degrees (see, for example, Exhibit C), and in any event at least 115 degrees C." Lewis Declaration, par. 14.

As for combining Maruno 1 and/or Maruno 2 with Groman (US 4,827,945) to result in substitution of autoclaving for filtration as the method of sterilization, Groman discloses autoclaving of superparamagnetic iron oxide complexes in the presence of the counterion citrate. As stated in Groman, "The use of citrate counterion also confers a distinct advantage to the fluids as it renders them highly stable. In fact, the citrated fluids can withstand autoclaving greatly facilitating sterile administration." See col. 9, lines 28-31. But Groman was filed in *1987*. Not quite four years later, an application was filed disclosing filter sterilization of a colloidal, superparamagnetic contrast agent (Josephson - US 5, 160,726). The Josephson patent included two of the inventors from the Groman patent, including Groman, but did not use autoclaving, as disclosed in the Groman patent. Why did the Josephson patent not use autoclaving, if autoclaving was so clearly superior to filter sterilization and FDA preferred? Because in the nearly four years from the Groman application, the inventors learned that autoclaving modified the superparamagnetic iron oxide colloids, resulting in a drop in blood pressure to patients, a highly undesirable adverse reaction. Josephson, col. 3, lines 62-67. Consequently in

1991, Josephson (and Groman and Lewis), advocated filtration as the method of choice for sterilization. See, for example, Lewis Declaration, pars. 8 and 10.

Surprisingly, as was seen with Maruno 1 and Maruno 2, where in spite of the issuance of the Josephson patent Maruno 2 chose to continue filtering as opposed to autoclaving the contrast agents, the very same inventor (Groman) who had previously advocated autoclaving now advocated filtration in the Josephson reference, in spite of the generally acknowledged ideal of autoclaving for terminal sterilization of contrast agents.

Maruno, Groman, Lewis, and Josephson are all skilled in the art, yet none chose to substitute autoclaving for filtration as the means for terminal sterilization after Groman's first use of such a method in 1987, despite knowing that it was the preferred method in almost every way. If such a substitution were obvious, would not one of them have followed Groman and chosen to make that substitution? The reality is that the very real risks of adverse affects associated with such a method of sterilization applied to the new materials prevented later inventors from autoclaving their superparamagnetic iron oxide contrast agents. Until the materials of the present invention, superparamagnetic iron oxide contrast agents could not be autoclaved without risks of adverse reactions.

E. 35 U.S.C. §103(a) requires motivation to combine, a reasonable expectation of success, and the prior art must teach or suggest all the claim limitations.

According to section 2142 of the Manual of Patent Examining Procedure (MPEP),

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach

or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Careful examination of the references shows that the Examiner has failed to set forth a *prima facie* case fails for obviousness. Given the factual background explained above, there is no basis for combining the references in formulating the rejection. As discussed above, the references teach consistently that the claimed subject matter would have been completely unexpected. The combinations of prior art references urged by the Examiner in rejecting the claims ignore problems with instability and adverse reactions associated with such combinations. As stated clearly in Dr. Lewis's Declaration, autoclaving led to deposition of particulates for many agents; or required the use of citrate, which frequently led to changes in the nature of the contrast agent resulting in a risk of edematous response; or required slow administration of dilute solutions making fast, high concentrations of the contrast agent in the subject difficult to obtain. See Lewis Declaration, pars 7-8.

The Examiner rejects all currently pending claims as unpatentable over Maruno 1 or Maruno 2 in view of Josephson or Lewis or Groman, in further view of Golman. But consider the history of disclosures. Groman (filed in 1987, with Josephson and Lewis) autoclaves, the only reference cited which does autoclave. Lewis (filed in 1988 with Groman and Josephson), goes back to filter sterilization, in spite of the Groman patent. Josephson (filed in 1992 with Groman) admits autoclaving is preferred, but warns against it and in fact still discloses, and advocates, filter sterilization for superparamagnetic iron oxide complexes because of risks associated with edematous response when such agents are autoclaved. Maruno 1 (filed in 1991) filter sterilizes. Maruno 2 (filed in 1997), chose

to continue filter sterilization. None of the references filed after Groman – not Lewis, Josephson nor Maruno 2, all involving inventors skilled in the art and readily aware of the desirability of autoclaving for sterilization – discloses autoclaving as the method for sterilization. Applicant respectfully submits that not only is there no motivation to combine Groman with Lewis, Josephson, Maruno 1 or Maruno 2, there is motivation not to combine such references. The fact that none of the inventors involved in the above references made such a combination, including Groman in the later Lewis and Josephson patents (when it was his own work that first advocated autoclaving) supports this position. All references cited by the Examiner for combination with Groman were filed after Groman issued, yet none discloses the use of autoclaving for sterilization.

Consequently, applicants respectfully submit that none of these prior art references, alone or together, teach the subject matter claimed herein: namely, a method for providing an iron oxide complex for administration to a mammalian subject, wherein terminal sterilization is done by autoclaving.

With respect to the combination of Maruno 1 or Maruno 2, with Groman, Lewis or Josephson, in further view of Golman (US 5,985,245), the previous arguments relating to combinations without Golman still apply. Therefore, finding motivation to combine Golman with other references that would not have been combined in and of themselves is even more unlikely, particularly when the additional reference (Golman) is so far from the relevant art.

For example, the kit of Golman requires "a physiologically tolerable manganese compound, kojic acid, or salt thereof, said first contrast agent having a manganese concentration of at least 0.3 mM or being in a dosage unit form containing at least 300

μmol manganese, and in a second container, a second contrast agent as defined in claim **1**." (i.e., a ferromagnetic or superparamagnetic material). See claim 6, col. 8 and claim 1, col. 7. The kit claimed and disclosed in Golman requires two MRI contrast agents. One is "a physiologically tolerable manganese compound ...." and the other is "a *particulate* ferromagnetic or superparamagnetic material." See col. 7, claim 1, emphasis added.

In contrast, the present application includes claim 56 directed to a kit having a single MRI contrast agent – a carboxymethylated reduced ultrasmall superparamagnetic iron oxide colloid – that is <u>not</u> particulate, but rather, is an ultrasmall colloidal suspension that specifically does <u>not</u> form a particulate because particulate formation is undesirable (*vide supra*, p. 6, par. 1, and Application, p.11, lines 14-23). In addition, the claim 56 is directed to a kit for only an iron oxide complex, and there is no disclosure or requirement for a manganese-based MRI agent. Also, the invention of claim 56 requires that the contrast agent in the kit be terminal sterilized by autoclaving (claims 53 and 54, from which kit claim 56 depends). As argued above, there is no motivation for combining Maruno 1 or Maruno 2 (filter sterilization) with Groman (autoclaving) or Lewis (filter sterilization) or Josephson (filter sterilization) with still another reference disclosing filter sterilization, i.e. Golman. The only thing that Golman stands for is a kit with MRI contrast agents. The Golman agents are not autoclaved, the kit requires two contrast agents, including a manganese contrast agent, and the other contrast agent, although iron-based, is specifically defined as a particulate. The combinations suggested by the Examiner "in further view of Golman" are far-fetched and unsupported by any indication of motivation from the Examiner to make such combinations.

Some mention should also be made specifically of claim 35 and subsequent, because the Examiner's rejection of these claims makes no sense. Claim 35 is directed to an improved method of administering a polysaccharide of the type wherein there is a risk of an edematous response, and the improvement provides decreased edematous response. Nothing in the art remotely addresses the problem addressed by this claim. And there is no prima facie basis for the art rejection.

For the reasons set forth above, Applicant respectfully submits that claims 1-13, 18-29, 35, 36, and 39-66 are not rendered obvious by the teachings of Maruno 1 or Maruno 2 in view of Josephson or Lewis or Groman, in further view of Golman because there is no motivation to combine these references to arrive at the claims of the present invention. Therefore, Applicant respectfully submits that all pending claims are not obvious.

II. The application as amended satisfies §§ 132 and 112.

Regarding the objections to new matter under 35 USC § 132, the phrase "at doses in vast excess, for example, 100 mg/kg body weight" was deleted from page 1, lines 25-26, in the Background section.

Support for the phrase "at higher dose" on page 17, lines 20-21 can be found in the specification on page 46, lines 10-12.

Support for the phrase "at doses in vast excess" (p.19, lines 22-23) can be found by comparing page 46, lines 10-12 ("The dose administered in these studies was 100 mg Fe/kg body weight, a dose much greater than that used as an imaging agent in rats, pigs, and humans (see Examples 53-56)") and page 47, lines 21-22 ("The dose administered in these studies was, as above, 100 mg test substance/kg body weight") to studies described

in the specification on page 49, lines 19-20 ("An MRI scan of a rat taken shortly after administration of 5 mg of CMRD coated USPIO (Example 31) per kg body weight is shown in Figure 6B.") and lines 26-27 ("Four doses of 0.4, 0.8, 1.6, and 2.2 mg of iron/kg body weight of sample (Example 31) were administered to the pig in sequential order."); and page 51, lines 13-15 ("The trial design employed thirty-five human subjects each administered one dose of CMRD T10 coated USPIO prepared according to Example 31 (i.v.; 1-4 mg of iron/kg body weight).") and lines 19-20 ("No adverse reactions attributable to administration of the composition were observed among the treated subjects at any dose, including the highest dose (4 mg/kg)."). As one can easily recognize, doses of 100 mg/kg of body weight are more than 20 times greater than the highest dose (5 mg) of iron oxide complex administered in comparative tests, and more than 250 times greater than the lowest dose (0.4 mg) administered. Applicant respectfully submits that doses that are between 20 times to 250 times greater than doses administered in control tests are justifiably described as doses "in vast excess" Thus, applicant respectfully submits that adequate support for using these phrases is present in the application.

Similarly, support for the phrase "administered in vast excess to" on page 45, line 22 can be found by comparing the same text on page 46, lines 10-12 and page 47, lines 21-22, to studies described in the specification on page 49, lines 19-20 and lines 26-27; and page 51, lines 13-15 and lines 19-20. Therefore, it is respectfully submitted that abundant support for the added phrases is present in the specification and that no new matter has been added to the application.

In response to 35 U.S.C. § 112, paragraph 2 objections, applicant has requested that the following text be inserted into the Summary, page 3, line 4, after the sentence that ends with "carboxylation." and before the sentence that starts with "Further according to....":

> "The term "derivatizing" and related terms (e.g. derivatives, derivatized, derivatization, etc) refer to the conventional sense of functionalization at the reactive sites of the composition."

The term derivatizing, and all its related forms, was defined by an amendment to the Specification, to refer to the conventional sense of functionalization at the reactive sites of the composition. Such an amendment, and the above insertion of text to the Summary, is not addition of new matter because the terms are merely being defined as one skilled in the art would ordinarily interpret them. The Examiner has objected to such terms for reasons of vagueness and indefinites, yet to one skilled in the art, it is clear where derivatization of any given composition will occur. As one skilled in the art is aware, functionalization to produce derivatives occurs at the most reactive site on a molecule, the site termed the functional group. Lewis Declaration, par. 16.

It is not necessary to state explicitly that this will be the site of derivatization, because a person skilled in the art would already know this. Lewis Declaration, par. 16. For example, *Solomon's Organic Chemistry, Sixth Edition*, John Wiley & Sons, Inc., New York, (1996) p. 65 states "A functional group is the part of the molecule where most of its chemical reactions occur. It is the part that effectively determines the compound's chemical properties (and many of its physical properties as well). The functional group of an alkene, for example, is its carbon-carbon double bond." The functional group of an alcohol is the hydroxyl group, as defined in *Solomon's Organic Chemistry*, "Methyl

alcohol .... is the simplest member of a family of organic compounds known as **alcohols**. The characteristic functional group of this family is the hydroxyl (OH) group ...." (id. p. 67). Lewis Declaration, par. 16. In the present invention, the reduced polysaccharide is a poly alcohol compound; thus, it contains multiple OH groups. All the OH groups are functional groups and thus potential reactive sites to form derivatives of the original compound. Lewis Declaration, par. 16.

But in spite of the multiple OH groups, the possibilities for reactions and resulting derivatives with such a compound are limited, because as one skilled in the art would understand, there are a limited number of reactions that occur with alcohols. Lewis Declaration, par. 17. As summarized in *Organic Chemistry, Second Edition* by K. P. C. Vollhardt and N.E. Shore, W. H. Freeman and Co., New York (1994), pp. 278 there are basically four types of reactions that occur with alcohols: 1) reactions in base; 2) reactions in acid; 3) elimination reactions; and 4) oxidation reactions. Examples of compounds that can be formed as derivatives of alcohols include ethers, esters, acids, amides, and haloalkanes (via acid/base chemistry), aldehydes, ketones and acids (via oxidation reactions), and alkenes (via elimination reactions). Those are essentially all the derivatives one skilled in the art would envision for an alcohol. Therefore, the number and types of derivatives that can form from alcohols is finite, and consequently, using such terms as derivative or derivatizing within the context of this application is not vague and indefinite to one skilled in the art of basic organic chemistry. Lewis Declaration, par. 17.

In fact, such terms are used in the very references cited by the Examiner for obviousness rejections. For example, Maruno 2 (US6,165,378) states in the abstract:

"The present invention provides a polysaccharide-magnetic metal oxide complex consisting of a polysaccharide derivative obtained by …." The term derivative is referred to throughout the document and is never defined per se. The term even shows up in the claims. For example, Claim 1 states: "A complex of a magnetic metal oxide and a polysaccharide derivative, wherein the derivative is obtained by carboxyalkyl-etherifying and aminoalkyl-etherifying a polysaccharide, where the aminoalkyl is optionally-substituted." See col. 19. Lewis Declaration, par. 18.

Not only does this patent claim a derivative of a polysaccharide, but the derivative is obtained by more than one type of chemistry (making the potential products less determinable, in an absolute sense) and is further muddied by the "optionally substituted" aminoalkyl that may be chosen for the aminoalkyl-etherifying derivatization. The point is not that Maruno 2 used it so we can too. The point is that Maruno 2 used the term derivative because it is a term *readily understood* by those skilled in the art.

Further, the application discloses (p. 22, lines 20-22), and claims (claims 27-29), the derivatives of the present invention, for example carboxyalkylated polysaccharides, in terms of overall amount of derivatization per gram of starting material – i.e. "about 900 μmole of carboxyl groups per gram of polysaccharide" – see claim 27. A person skilled in the art would understand the scope of such a disclosure or claim; it is not necessary to list every possible, stereochemically-defined derivative product for a person skilled in the art to understand what is meant by these terms. This method of defining products by percent reaction is also standard within the art of chemistry, and further defines the terms derivatives, and derivatized products, to those skilled in the art. For example, Maruno 1 (again, a reference cited by the Examiner for obviousness rejections) describes a

substituted polysaccharide, and how to determine the degree of substitution in a similar way. Maruno 1 states that "the substitution degree of the polysaccharide carboxyalkyl ether is calculated from the amount of consumed sodium hydroxide as mole number per monosaccharide unit." See col. 3, lines 6-9.

Unlike a molecule with multiple types of functional groups where it ~~is~~ might be unclear which derivatives form depending upon which functional group is most reactive, in the present invention, the only reactive group in the polysaccharides is the OH group. Any derivatization reaction, whether it is acid/base chemistry, elimination, or oxidation, will result in the same reaction at every single OH group – to the extent that the reaction goes to completion. Thus, by describing the derivatized polysaccharides in terms of grams of (derivative) group per grams of starting material, the applicant respectfully submits that the compounds of the present invention have been described in the simplest, clearest, and most readily understood terms for one skilled in the art.

In light of the finite number of reactions and derivatives that can form from alcohols, the common knowledge among those skilled in the art concerning where derivatization reactions will occur on the polysaccharides, and the common usage of the term derivative within the applicable art, applicants respectfully submit the term "derivative" and its analogs is a well-known term of art, and therefore, that all claims utilizing the terms derivatized, derivatives, derivatized, derivatizing, derivatization, etc, are now in condition for allowance with respect to those related terms. Those claims are 5, 10-12, 22, 22, 26-29, 35, 36, 57, 59, and 64-66.

Claim 45 has been amended to eliminate the word "enhanced," a term the Examiner objected to as relative and thus indefinite. Support for this amendment is found on page 4, lines 12-14 and page 49, lines 19-21.

The term "ultrasmall" was also cited by the Examiner as relative, and therefore indefinite. This term is found in claims 53 and 54. Although applicant argued in Response A (see Response dated October 4, 2001, p 14, last paragraph et seq.) that "ultrasmall" is adequately defined within the specification of the present application, the Examiner was not persuaded. Applicant herein provides additional reasons for the specificity of the term.

On page 10, lines 14-19, the present application reads "Combidex® (Advanced Magnetics, Inc.) is a dextran coated ultrasmall superparamagnetic iron oxide (USPIO) which has completed Phase III clinical trials for both liver imaging and Phase III trails for lymph imaging. Combidex® has a smaller mean diameter (20 nm) than Feridex I.V.® (60 nm), which gives it a different biodistribution in humans." Next, the Examiner is directed to the present application, pages 33 and 35, Tables 4 and 5, respectively. Both Tables compare properties of iron oxides made with native or reduced polysaccharides. Both tables provide the mean volume diameter (MVD) of these particles. Glancing at the Tables, one can see that the MVD for the iron oxides made from the reduced polysaccharides range from 16 to 21 nm (Table 14) or 12-18 nm (Table 5). The figure legend for Table 4 states "Comparison of properties .... under conditions that form a USPIO with reduced polysaccharides" and that for Table 5 states "Magnetic susceptibility and particle size .... under conditions to give particles of less than 30 nm MVD ...."

In addition, the term is not newly used in this application. The Lewis Patent (incorporated by reference in the present application) discloses a reference by R. Weissleder entitled "Ultrasmall Superparamagnetic Iron Oxide: Characterization of a New Class of Contrast Agents for MR Imaging," *Radiology*, 75:489-493 (1990), (see U.S. Patent No. 5,055,288, p.2, Other Publications). Lewis Declaration, par. 19. The original Weissleder paper describes a new class of contrast agents "small enough to migrate across the capillary wall, a prerequisite in the design of targetable particulate pharmaceuticals." See Abstract. Since this 1990 Weissleder publication, this new class of contrast agents, and the name for the class, abbreviated USPIOs, is cited throughout the contrast agent literature. For example, a quick search in the journal *Radiology* alone yielded five abstracts using the term "ultrasmall superparamagnetic iron oxide," from 1998 to the present. Lewis Declaration, par. 20. See abstracts, Exhibit I to the Lewis Declaration. Dr. Lewis himself describes Combidex® as "a complex of ultrasmall particles" (see Lewis Declaration, par. 8) and the third generation materials claimed in the present application as "a complex of ultrasmall particles" (id. par. 9).

For the forgoing reasons, in particular in light of the Weissleder 1990 *Radiology* article identifying a new class of contrast agents — superparamagnetic iron oxides — and the numerous usages in the art thereafter — Applicant respectfully submits that the term is widely known and understood by those skilled in the relevant art and is therefore not indefinite. As such, with respect to the 35 U.S.C. § 112, paragraph 2 rejections, applicant respectfully submits that all claims are now in condition for allowance.

CONCLUSION

For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

The applicants hereby petition for a three-month extension of time, and a check for $830 which includes the fee for the three-month extension as well as the RCE filing fee. Please charge deposit account number 19-4972 for any additional fees that may be required for the timely consideration of this application. The Examiner is requested to telephone the undersigned if the application is not in condition for allowance, to schedule an interview prior to the office action.

Date: April 25, 2002

Respectfully submitted,

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